Rhabdomyosarcoma: The Experience of Single Institution

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ABSTRACT

This study is a retrospective analysis of the treatment results of pediatric rhabdomyosarcoma patients who attended the pediatric unit of Kasr-EI-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) from January 1992 to January 2001. Fifty-five new cases of pediatric rhabdomyosarcoma attending the pediatric unit outpatient clinic of (NEMROCK) were evaluated. Males constituted 63.6% of the cases (35 cases) and females 36.4% (20 cases). The median age was 6 years and the ages of the patients ranged from 1 to 9 years. (For Stages, this disease was diagnosed in most of the cases in early stages (40/55, 72.7%) versus late stages (15/55, 27.3%). This is because the most common site in this study was the head and neck, which causes early parental notification). Pathologically, embryonal type was the commonest statistically (48/55, 87.3%) compared to the alveolar type (7/55, 12.7%). Concerning site of the primary tumor it was found to be highest in the head and neck (20/55, 36.4%) followed by abdominal site (23.6%) excluding the genitourinary system which was classified separately because it included pelvis and abdomen (13/55, 23.6%). The estimated 5-year Failure Free actuarial Survival (FFSR) for the entire study is 68% (n = 55; 95% confidence interval [CI], 63% to 73%), and the estimated 5-year overall actuarial survival (OS) rate is 74% (95% CI, 69% to 79%). Twenty cases experienced relapse during the 5 years follow up (i.e. 36.4%). No lost follow up in the selected group of children studied. In addition, only 3 cases showed distant metastasis at the onset of the study. Complete remission (CR) was achieved in 50.9% of the cases.

Despite the advances in the therapy of rhabdomyosarcoma, Nearly 30% of pediatric cases with rhabdomyosarcoma experience progressive or relapsing disease, which has a fatal end. The factors determining the 5-year survival after relapse at the time of initial diagnosis include histological subtype, and disease group. These findings will form the basis of a multi-institutional risk adapted relapse protocol for childhood rhabdomyosarcoma patients.

Keywords: Rhabdomyosarcoma, embryonal, alveolar.

Introduction

The annual incidence of rhabdomyosarcoma (RMS) in children 18 years of age or younger is 4.3 cases per million children, with approximately 350 new cases diagnosed in the United States each year. Among the extra-cranial solid tumors of childhood, RMS is the third most common neoplasm after neuroblastoma and Wilm's tumor. Almost two-thirds of cases of RMS are diagnosed in children aged 6 years or younger, with a smaller incidence peak in early-mid adolescence. The tumor is slightly more common in boys and males (11.8 per million) than in girls and females (10.3 per million) (4). An international study confirmed previous reports of racial and gender differences in the incidence of RMS (4).

Although these tumors may arise virtually anywhere in the body, certain distinctive clusters of features emerge regarding age at diagnosis, site of primary tumor, and histology. For example, head and neck tumors are most common in children younger than 8 years of age. Especially if arising in the orbit, they are usually of the embryonal variety. On the other hand, extremity tumors are seen more commonly in adolescents and are more frequently of the alveolar subtype. A unique form of RMS arising from the bladder or vagina; the botryoid variant (so named because of its resemblance to a protruding cluster of grapes) is seen almost exclusively in infants.
The development of increasingly intensive, large-scale, international, collaborative, multimodality therapeutic protocols for treating these tumors, particularly the Inter-group Rhabdomyosarcoma Studies (IRS), has led to a steady improvement in the curability of these neoplasms, especially for the group of patients with locally extensive irresectable tumors. Along with the improvements in outcome, there has appeared an increase in both short- and long-term sequelae of therapy (3).

**Aim of the study:** is to evaluate the treatment results of pediatric Rhabdomyosarcoma patients treated in our department, and to assess by uni- and multi-variant analyses the most important prognostic factors affecting treatment and prognosis.

**Patients and methods**
This study is a retrospective analysis of the results of treatment of new pediatric Rhabdomyosarcoma patients who attended at the outpatient clinic of the pediatric unit of Kasr-el-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) from January 1992 until January 2001.

All cases were subjected to various surgical modalities including surgical biopsy, partial excision, and complete excision of the tumor and the diagnosis was confirmed by pathological examination, the patients were divided into favorable histology (FH) which is considered the embryonal subtype and unfavorable histology (UH); considered the alveolar subtype.

All cases were subjected to clinical history taking including family history of the disease and history of consanguinity and careful physical examination. Laboratory investigations including complete blood picture (CBC), renal and liver profiles, cerebro-spinal fluid cytology (CSF) in head and neck rhabdomyosarcoma cases were performed. Radiological investigations including chest X-ray (CXR), abdomino-pelvic sonography, post-operative CT scan to exclude recurrence and/or residual disease were done routinely. Patients were divided into 4 groups according to the clinical staging system employed in the Intergroup Rhabdomyosarcoma Studies I through III (table 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>Localized disease, completely resected:</th>
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<tbody>
<tr>
<td></td>
<td>A. Confined to organ or muscle of origin.</td>
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<td></td>
<td>B. Infiltration outside organ or muscle of origin.</td>
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<tr>
<th>Group</th>
<th>Compromised or regional resection, including:</th>
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<tr>
<td></td>
<td>A. Grossly resected tumors with microscopic residual tumor.</td>
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<td>B. Regional disease, completely resected, with nodes involved, and/or tumor extension into an adjacent organ.</td>
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<tr>
<td></td>
<td>C. Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual tumor.</td>
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<th>Group</th>
<th>Incomplete resection or biopsy with gross residual disease remaining.</th>
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<th>Group</th>
<th>Distant metastases present at onset.</th>
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Patients were divided into low-risk and high-risk:

**Low-risk patients included cases with the following criteria:**
1) Favorable histology.
2) Stage I and II disease.
3) Age ranging from 1-10 years.
4) Favorable sites as the orbit, paratesticular area, head & neck excluding infratemporal & parameningeal regions and the genitourinary tract with exclusion of the urinary bladder and prostate (4,5,6,7).

**High-risk group included cases with the following criteria:**
1) Unfavorable histology.
2) Stage III, IV disease.
3) Age > 10 years.
4) Unfavorable sites as para-meningeal, retro-eritoneal sites and extremities especially with alveolar histology (4,5,6,7).

Patients with stage I, II orbital and stage I paratesticular area embryonal disease received 32 weeks of vincristine 1.5 mg/m2 weekly, actinomycin-D 0.013 mg/Kg day 1 to day 5 every 21 days without radiation therapy (8). Other sites received 52 weeks of chemotherapy and radiation therapy on week 13 with 4140 cGy for stage I and II, and 5040 cGy for stage III and IV by conventional fractionation radiation therapy (CFR) and the treatment volumes included the tumor bed and a 2 cm safety margin at least (9,10). Chemotherapy regimens included VAC (vincristine 1.5 mg/m2 weekly, actinomycin-D 0.015 mg/Kg/day day 1 to day 5 and cyclophosphamide 2.2 gm/m2 IV with mesna every 21 days), VAI (vincristine, actinomycin-D and ifosfamide 1.8 gm/m2 IV day 1 to day 5 and mesna every 21 days) or VIE (vincristine, ifosfamide and etoposide 100 mg/m2.
I.V day 1 to day 5 every 21 days) \(^{11,12}\). Relapsing cases received palliative radiation therapy and second line chemotherapy (cisplatinum I.V 100 mg/m\(^2\) divided over 2 days, vepesid 100 mg/m\(^2\) I.V day1 to day 3 to be recycled every 21 days) for 6 cycles \(^{10}\).

The patients were followed-up every 3 months for 5 years with a median follow-up period of 36 months by CXR, abdomino-pelvic sonar, C-T scan, cerebrospinal fluid cytology for head and neck cases and liver and kidney profiles. The overall survival, (time from date of diagnosis until date of death or last follow up), disease free survival (DFS time from date of complete response until time of documented radiological and clinical relapse) and complications of treatment were assessed according to the WHO criteria and statistically analyzed. Correlation between various prognostic factors with survival and disease free survival (DFS) was done.

The response to treatment was assessed as complete response, CR (complete resolution of the original disease), partial response, PR (> 50% reduction of the original disease), stable disease and disease progression.

**Statistical methods**

The Kaplan Meier method was used to estimate overall survival and disease free survival. Assessment by uni- and multi-variant analyses of the most important prognostic factors affecting treatment and prognosis was done. The log rank test was applied to compare the different groups (P-value is significant at 0.05 level) \(^{10}\).

**Results**

This study included 55 cases of pediatric rhabdomyosarcoma and we found that; the most common age was between 1 and 9 years old (36/55, 65.5%). In addition, this disease is significantly higher in boys (35/55, 63.6%) than girls (20/55, 36.4%). Concerning the site of the primary tumor it was highest in the head and neck (20/55, 36.4%) followed by abdominal sites (23.6%) excluding the genitourinary system (13/55, 23.6%) which was classified separately because it included the pelvis and the abdomen. Pathologically, embryonal type was the commonest (48/55, 87.3%) compared to the alveolar type (7/55, 12.7%). The size of the tumor was <5 cm in 25 cases (45.5%) and > 5 cm in 30 cases (54.5%) . Regarding the various stages, this disease was diagnosed in most of the cases in early stages (40/55, i.e. 72.7%) versus late stages (15/55, 27.3%). This is because the most common site here in this study was the head and neck, which causes early parental notification (table 2).

Concerning treatment, table (1) shows the classification according to surgical procedures. Added to that 19/55 (34.5%) were treated by radiotherapy given on a post-operative adjuvant setting.

As regards overall response to treatment: 41/55 (74.5%) were responders, 28 (50.9%) achieving a complete response and 13 (23.6%) a partial response. Disease progression occurred in 12 cases (21.8%). Out of the responders, 20/55 (36.4%) relapsed during the 5 years of follow up, mainly within the first 30 months, 15 as local failure and 5 as distant metastasis.

<table>
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<th>Table (2): Demographic Data</th>
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<tr>
<td><strong>Factor</strong></td>
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<td>Head and Neck:</td>
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<td>Nasopharynx</td>
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<td><strong>Pathological:</strong></td>
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The estimated 5-year Failure Free actuarial survival (FFSR) for the entire study is 68% (n = 55; 95% confidence interval [CI], 63% to 73%), and the estimated 5-year overall actuarial survival (OS) rate is 74% (95% CI, 69% to 79%). Twenty cases experienced relapse during the 5 years follow up (i.e. 36.4%). There were no lost follow-up cases in the selected group of children studied (Fig. 1). In addition, only 3 cases showed distant metastasis at the onset of the study.

Uni-variant Analysis of total actuarial survival:
On the other hand, according to grouping, it has been found that survival in group I (at 30 months) was found to be 100% (CI=100%), in group II 89% (CI=84-94%) and in group III 79% (CI=75-83%) with a statistically significant difference between the three groups (Fig. 2). On the other hand, total actuarial survival according to pathological type and groups showed statistically higher median survival for embryonal type compared to alveolar type. I.e. children with embryonal histology and treated by complete surgical excision with free surgical margins and -ve LNs showed the highest survival (100%) compared to the rest. However, if surgical margins or LNs showed microscopically residual as seen in group II or III, the embryonal histology showed statistically higher values of survival compared to those with alveolar histology 95%, (CI=93-97%) and 83%, (CI=79-87%) respectively versus 83%, (CI=79-87%) and 77%, (CI=71-83%) (P<0.05) (Fig.3, 4).

Uni-variant analysis of Failure Free Survival:
According to grouping, it has been found that FFS was statistically higher in group I: FFS 95%, (CI=90-100%) compared to group II: FFS 85%, (CI=81-89%) and P<0.05% and group III: FFS 65%, (CI=55-73%) and P<0.001. On comparing group II and III the P value was <0.01 (Fig. 5). On the other hand, when histological types were added to the grouping. It was found that the failure rate increased in the three groups with the note that, in group I; it was of marginal statistical difference between the embryonal type: FFS 96%, (CI=92-100%) and alveolar type: FFS 85%, (CI=79-91%) (P=0.05%). Whereas, it was statistically higher for group II FFS: 90%, (CI=82-95% versus FFS 77%, (CI=69-82%) and p<0.01, for group III the difference was insignificant FFS 78%, (CI=74-82%) versus FFS 72%, (CI=67-77%) respectively, and p>0.05. Meanwhile, the difference between the FFS for group II and III was insignificant in the embryonal histology but it was statistically significant in the alveolar type (Fig. 6, 7).

Radiotherapy and children of groups II and III:
Nineteen cases of both groups had been treated with conventional radiotherapy and it had been found that radiotherapy had no effect on the total actuarial survival when compared with those children not treated with radiotherapy OS 85%, (CI=78-92%) versus OS 79%, (CI=69-89%) and P>0.05. On the other hand, radiotherapy affected the failure free survival period where the incidence of failure was statistically higher in patients not treated with radiotherapy. Failure free survival for those treated with radiation was 84%, (CI=80-88%) versus 69% for the non-irradiated, (CI=64-74%), and P<0.05 (Fig. 8, 9).

Relapse and end point results:
It has been found that failure affected survival significantly in such a way that local failure made a significant drop in total actuarial survival from 90% (CI=87-93%) to 80% (CI=75-85%) and P<0.001. Further still a statistically significant drop in total actuarial survival was observed with distant metastasis and it was found to be 44% (CI=39-49%) and P<0.001 (Fig. 10).

Multivariate Analysis:
Multivariate analysis showed that the most predictable favorable factors in the management of rhabdomyosarcoma were type of surgery (grouping in this study), histology, staging of the disease and favorable primary sites (head and neck, and genitourinary tumors). This can be summarized in the following table: (3)
From the above table, children of group I with embryonal histology and favorable primary sites showed the highest overall survival of 88% (CI=85-91%), and survival significantly dropped to 74% when the cases had unfavorable sites of disease (70-78%). Similarly, survival significantly dropped in children with alveolar histology. What is more important is that the unfavorable sites affected significantly children of group III who suffered a significant drop in survival in both histology types, from a survival of 74% and 62% to 38% and 25% respectively.

For Failure Free Survival, Multivariate Analysis showed:
The most important predictive favorable factors for FFS included a tumor size less than 5 cm, (P = 0.001) early stages, (I and II) (P=0.01), favorable primary sites, (of head and neck and genitourinary) (P=0.001) and radiotherapy treatment (P=0.01). On the other hand age, (P=0.44) sex, (P=0.90), and histology (P=0.30) were not predictive of FFS.

Discussion
In this study, males constituted 63.6% (35 cases) and females 36.4% (20 cases) and history of consanguinity was present in 5.45% (3 cases). These results are close to the work of Ruymann where males constituted 71.4% of the cases and females 28.6% of the cases; and history of consanguinity was present in only 9% of the cases. The most common site of involvement was the head and neck 36.4% (20/55), followed by the abdomen and the genitourinary tract, with the same incidence of 23.6% (13/55), and finally the extremities, 16.3% (9/55). This contrasts with the work of Akyuz where the pelvi-abdominal area was the most common site of involvement (29%), followed by the extremities (15%), and then the trunk and the lung (5%). Moreover, Nakada found that the most common site of involvement was the pelvis (27.3% of cases), then the abdomen (23.8%), and then the head and neck (21.4% of cases).

In our present study stage I cases constituted 3.6% (2 cases), stage II 69.1% (38 cases), stage III 21.8% (12 cases) and stage IV 5.4% (3 cases). Contrary to that, Raje who performed a similar study stated that stage I cases constituted about (10%), stage II (62.7%), stage III (20.2%) and stage IV cases (7.1%).

In the present study, embryonal histology constituted 87.3% of the cases (48 cases) and alveolar histology 12.7% (7 cases) unlike the work of Callender; where embryonal histology constituted about (43.2%) of the cases, alveolar histology (40.5%) of the cases, mixed histology (2.7%), and unclassified histology in (13.5%) of cases.

In the present study stage I, II orbital and stage I paratesticular disease cases with favorable histology received 32 weeks of vincristine, and actinomycin-D. Other sites received 52 weeks of chemotherapy VAE, VAI or VIE. Radiation therapy was given on week 13 with 4140 cGy for stage I and II, and 5040 cGy for stage III and IV by conventional fractionation radiation therapy (CFT) using a cobalt 60 or a 6 MV linear accelerator. The treatment volumes included the tumor bed and a 2 cm safety margin at least. This is similar to the work of Crest where early stage orbital and paratesticular area disease received vincristine and actinomycin-D, other stages received VAE, VAI or VIE, radiation therapy was also given at a dose of 35-54 cGy according to stage.

In the present study the 5-year overall survival was 74% and disease free survival was 68%, in comparison to Crest where the 5-year survival was 77% and 4-year DFS was 76%. Also, with the work of Flamant who attained a 5-year overall survival of 68% and a 5-year DFS of 55%.

In our present study the 5-year, overall survival for embryonal histology was 80.6% and 65% for alveolar histology; these results correlate with the work of Anderson where the 5-year survival for embryonal histology was 64%, and for alveolar histology, it was 26%.

The 3-year overall survival for patients less than 10
years old was 55.7% and for those more than 10 years 45.5%. These figures were similar to the study of Laquaglia (23) and that of Armdt (24); where the age of the patient whether less than 10 years or more than 10 years had an impact on the 3-year survival. All the studies agreed that patients aged 1-9 years had the best 5-year survival (with results ranging from 81-98%). This study also agrees with the findings of Crest (20) where patients with para-testicular primaries had poorer outcomes if they were older than 10 years. The 3-years DFS was 63% for patients older than; versus 90% for patients younger than 10 years of age. It also agrees with the results of Chin (25) who found that long-term survival was noticed in patients younger than 10 years and with the work of Simon (26) who found that patients younger than 11 years of age have the best overall survival.

In the present study, the 3-year overall survival and DFS for favorable sites was 51% and 50%, whereas it was 23.08% and 20% for unfavorable sites respectively. This supports the work of Flamant (21) where the 5-year survival for favorable sites was 86% and the 5-year DFS was 52%. In addition, Akyuz (16) found that the overall 10-year survival for pediatric rhabdomyosarcoma patients was 42% and the best results were obtained in patients with orbital and genitourinary sites, especially with stages I-II and 1 to 5 years of age. Contrary to our results was the work of Ruymman (15) where he found no significant difference in survival among patients with favorable and unfavorable sites.

In the present study the 5-year overall survival and DFS for groups I, II, and III was 86%, 77% and 65% respectively; this coincides with the work of Andrassy (27) where the 5-year survival for group I RMS was 70%, for group II 65% and for group III 55%. In addition, the work coincides with the work of Akyuz (16) who reported the best survival results for patients with stages I and II.

The 5-year survival for our patients receiving radiotherapy was 84%, and for patients receiving no radiation therapy 74%. This agrees the report of Oberlin (28) in that there is no difference in overall survival regarding the implementation of radiation therapy as a part of initial treatment. However Wolden, (9) who conducted a pediatric rhabdomyosarcoma study, stated that patients with alveolar histology who received radiation therapy had a greater 10-year survival (82%) versus those who did not (52%).

Our 5-year survival for local relapse was 70% and for distant failure, it was 30%. This is similar to the work of Pappo (22) where the 5-year survival for local relapse was 65% and for distant failure, 25%.

Complete remission occurred in 28 cases (50.9%), partial response in 13 cases (23.6%), stable disease in 2 cases (3.6%) and disease progression in 12 cases (21.8%). This contrasts with the work of Frascella (29) where 2 patients achieved complete remission, 41 patients showed partial remission and 3 cases showed disease progression.

Relapse occurred in 20 cases (36.4%). Fifteen cases relapsed locally (27.3%) and 5 cases relapsed metastasizing distantly (9%), this coincides with the work of Wolden (9) where 6% of the failure sites were local, 6% were regional and 7% were distant.

Grade (I) hematological toxicity was present in 100% of cases, 30% experienced grade III leucopenia and 20% experienced grade II thrombocytopenia. Mucositis occurred in 20% of the cases and infections in 10% of the cases. This coincides with the work of Stewart (30) where toxicity was mainly hematological, mucositis and infections were not severe. No toxic deaths were reported.

**Conclusion**

Despite advances in the therapy of rhabdomyosarcoma, nearly 30% of pediatric cases experience progressive or relapsing disease, which eventually has a fatal end. The factors determining the 3-year survival after relapse at the time of initial diagnosis include histological subtype, disease risk group including age and stage. We also believe that present high risk rhabdomyosarcoma treatment protocols results are unsatisfactory regarding the complete remission rates and the survival indices; so further treatment intensification and may be newer drugs should be taken into consideration to manage those patients. Careful identification of the risk of the patient before initializing treatment is a cornerstone for the success in management. All high-risk patients should be subjected to new investigational therapy in an attempt to improve their outcome. In addition to this, we believe that the role of radiation therapy on an adjuvant basis needs to be further investigated. These findings will form the basis of a multi-institutional risk adapted protocol for new cases of childhood rhabdomyosarcoma patients and protocols for relapsing patients.
Fig.(1): Total Actuarial Survival and Failure Free Survival Of All Cases.

Survival

Follow Up In Months

- SURVIVAL - ▲ FAILURE FREE

Fig.(2): Total Actuarial Survival According to Patients Groups.

Survival

Follow Up In Months

- Group I - Group II - ▲ Group III

Fig.(3): Total Actuarial Survival According to Patients Groups with Embryonal Histology

Survival

Follow Up In Months

- Group I - Group II - ▲ Group III

Fig.(4): Total Actuarial Survival According to Patients Groups with Alveolar Histology

Survival

Follow Up In Months

- Group I - Group II - ▲ Group III

Fig.(5): Failure Free Actuarial Survival According to Patients Groups.

Survival

Follow Up In Months

- Group I - Group II - ▲ Group III

Fig.(6): Failure Free Actuarial Survival According to Patients Groups with Embryonal Histology

Survival

Follow Up In Months

- Group I - Group II - ▲ Group III

Fig.(7): Failure Free Actuarial Survival According to Patients Groups with Alveolar Histology

Survival

Follow Up In Months

- Group I - Group II - ▲ Group III

Fig.(8): Total Actuarial Survival of patients of groups II and III According to Treatment with or without Radiotherapy.

Survival

Follow Up In Months

- Group I - Group II - ▲ Group III

RT=Radiotherapy

- TREATED WITH RT - ▲ NO RT

5yr Overall Survival =74%
5yr Failure Free Survival =68%

P<0.001

P<0.05

P<0.01

P<0.05

P<0.05

P<0.05

Median Survival =6 years

Median Failure Free Survival =4.5 years

P<0.01

P<0.05

Median Survival =5.1 years

P<0.05

P<0.01

P<0.05

4.7 ys

3.3 ys

P>0.05

3.7 ys

2.7 ys

P>0.05

3.2 ys

P=0.05

4.1 ys

P=0.05

4.5 ys

Median Survival =4.8 years

P<0.05

P<0.05

P>0.05


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